Adrenal tumours in cats and dogs

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Pheochromocytomas are catecholamine-producing neuroendocrine tumors arising from chromaffin cells of the adrenal medulla. They are considered rare in dogs and even more uncommon in cats.

Pheochromocytomas are potentially malignant and local invasion into the adjacent vessels and other tissues is seen in more than 50% of dogs, sites of metastasis are regional lymph nodes, spleen, liver, kidney, pancreas, lung, heart, bone and CNS. The tumors are usually slow growing. Size is extremely variable and ranges between a few millimetres and more than 10 cm in diameter.

Most tumors are unilateral, occasionally both adrenal glands are affected. They may coexist with cortisol-producing adrenocortical tumors, ACTH-producing pituitary tumors or other endocrine tumors.

Clinical signs are usually the result of catecholamine excess and/or rarely from the space-occupying or invasive nature of the tumor. Catecholamines bind to α- and β-adrenergic receptors and induce “fright, fight and flight” reactions. Important effects are: increase of heart rate and contractility, increase of blood pressure and respiration rate, relaxation of gastrointestinal tract and urinary bladder, increase of blood glucose and free fatty acids and increased alertness. In healthy dogs the content of the adrenal medulla is approximately 30% norepinephrine and 70% epinephrine. In dogs with pheochromocytoma the proportion of the hormones may be different from healthy dogs and norepinephrine may be the predominant secretory product. Hormone secretion may be constant or sporadic and is highly unpredictable.

The disease may occur at any age, however it is most commonly seen in older dogs. There are no apparent sex and breed predispositions. The clinical presentation is highly variable. Signs may be apparent several times per day or may only reoccur after days, weeks or months. Severity of the disease ranges from dramatic and life-threatening to very mild. Some pheochromocytomas are hormonally silent.

Clinical signs may be categorized as:

1. non-specific: anorexia, weight loss, lethargy
2. related to the cardio-respiratory system and/or hypertension: tachypnoe, panting, tachycardia, arrhythmias, collapse, pale mucous membranes, nasal-, gingival-, ocular hemorrhage, acute blindness due to retina detachment

3. related to the neuromuscular system: weakness, anxiety, pacing, muscle tremor, seizures
4. miscellaneous: polyuria/polydipsia, vomiting, diarrhoe, painful abdomen.
The most common signs are weakness and episodic collapse. Large tumors may cause abdominal distension, ascites and hind-limb edema. Intra-abdominal or retroperitoneal hemorrhage due to tumor rupture is also possible.
Hypertension is one of the hallmarks of the disease. However, hypertension is not pathognomonic for pheochromocytoma and is also frequently found in hyperadrenocorticism, which is one of the most important differential diagnosis.
Due to the episodic secretion of catecholamines hypertension is only present in approximately 50% of dogs by the time of examination. Typically systolic measurements are between 200 and 240 mm Hg, the maximum systolic blood pressure reported so far was 325 mm Hg.
Often pheochromocytoma is only considered after an adrenal mass has been detected by ultrasonography. No pattern of echogenicity or architecture is specific for pheochromocytomas, other adrenal masses e.g. cortisol-producing tumors may look alike.
CT and MRI are more sensitive than ultrasonography to identify adrenal masses and to characterize the extent of local invasion, however they also do not allow a discrimination between pheochromocytoma and other adrenal masses.
In humans, diagnosis of pheochromocytoma is mainly based on biochemical detection of excessive amounts of catecholamines (epinephrine, norepinephrine) and their metabolites (metanephrine, normetanephrine) in 24-h urine or in plasma. Although the question which test (urine or plasma) is best, is still somewhat controversial, plasma metanephrines tended to be recommended increasingly as test of choice. In dogs evaluation of those biomarkers for the diagnosis of pheochromocytoma has started only a few years ago. Since 24-hours urine sampling is impracticable under clinical conditions, measurements of urinary fractionated catecholamines and metanephrines was established in spot urine samples by expressing their concentrations as ratio to the urinary creatinine concentration. Urinary normetanephrine to creatinine ratio was shown to be the parameter, which differentiated dogs with pheochromocytoma best from healthy dogs and dogs with hypercortisolism. We are currently using a cut-off value of urinary normetanephrine:creatinine ratio of 4 times of normal as being diagnostic for

pheochromocytoma. However, lower values do not exclude the disease and repetitive testing may therefore be required. Sample collection and urine processing are subject to certain conditions, such as acidification, light protection, cooled or frozen storage. Close collaboration with the laboratory is therefore necessary.
A recent study investigated the performance of free normetanephrine and free metanephrine in plasma. Both parameters were significantly higher in dogs with pheochromocytoma compared to healthy dogs, dogs with adrenocortical tumours and dogs with non-adrenal diseases; whereas plasma free normetanephrine was the parameter which discriminated best. We recently compared the diagnostic performance of urinary and plasma catecholamines and metanephrines by evaluating healthy dogs and dogs with pheochromocytoma, hypercortisolism or non-adrenal disease. Discrimination of dogs with pheochromocytoma was superior with urinary and plasma normetanephrine compared to urinary and plasma metanephrine. The differences between the urinary and the plasma tests were however small. In conclusion measurement of normetanephrine is the preferred biochemical test for pheochromocytoma. As differences between the urine and plasma test are minor decision between both tests should be made based on available technical facilities and dog-specific reference ranges.
Adrenalectomy is the treatment of choice and should be performed as soon as possible. It has been shown that perioperative mortality decreases if dogs are pretreated with an α-adrenergic blocker (phenoxybenzamine) for at least 1 - 2 weeks before surgery. In dogs surviving the perioperative period survival for several years is possible.
Primary hyperaldosteronism was first described in 1983. Since then, the disease has been diagnosed with increased frequency. Although no data are available concerning the true prevalence, it is assumed that the disease is more common than initially thought. This hypothesis is based on data from human medicine, where increased disease awareness led to a more systematic screening of the hypertensive population resulting in a strong increase in prevalence. Primary hyperaldosteronism however, seems to be very rare in dogs.
In human medicine, 60 – 65% of patients have bilateral nodular hyperplasia of the zona glomerulosa while 30 – 35% has aldosterone-producing adenomas (aldosteronomas). Unilateral hyperplasia and carcinomas are rare. Typical findings are systemic hypertension, hypokalemia and metabolic acidosis. However, because

screening for the disease is becoming more systematic and the diagnosis is generally made earlier, the prevalence of hypokalemia is decreasing and nowadays the majority of patients are normokalemic at the time of diagnosis. Currently, 5 to 10% of the general hypertensive population and 20% of patients with severe or resistant hypertension are assumed to suffer from primary hyperaldosteronism. The degree of hypertension is usually moderate to severe, and patients with aldosteronoma tend to have higher blood pressure than patients with nodular hyperplasia.

The consequences of increased aldosterone concentration are retention of sodium and water in the distal and collecting tubules of the kidneys. This results in increased intravascular volume and increased urinary potassium and hydrogen excretion. Excessive concentrations of circulating aldosterone also induce vasoconstriction and lead to an increase in peripheral vascular resistance. The two central mechanisms responsible for the development of hypertension in primary hyperaldosteronism are expansion of plasma and extracellular fluid volume and increase in total peripheral vascular resistance. Aldosterone *per se* has pro-inflammatory and pro-fibrotic properties resulting in vascular, cardiac and renal lesions. The pathophysiology of aldosterone-associated hypertension in cats is thought to be identical to humans.

The majority of cats with primary hyperaldosteronism have been shown to have unilateral neoplasias (adenomas or carcinomas), while bilateral hyperplasia has been less frequently reported. Clinical signs include weakness with associated cervical ventroflexion, mydriasis and blindness because of hypertensive retinopathy; some cats also show polyuria/polydipsia.

Almost all cats described to date have been hypokalemic at the time of diagnosis. However, as in human medicine, it may be possible that hyperaldosteronism is overlooked in cats with normal potassium levels. A more systematic screening for primary hyperaldosteronism may improve diagnosis and thus increase the prevalence of the disease. Based on data available to date, the prevalence of hypertension in cats with primary hyperaldosteronism appears to be high. Blood pressure was recorded in 30 cases, 26 of which were hypertensive. The severity ranged from mild to severe (185-270 mmHg), and the most common sequels were retinal detachment and ocular bleeding. Diagnosis requires demonstration of inappropriately elevated aldosterone concentration with low plasma renin activity (e.g. elevated aldosterone-to-renin ratio). Another test, the urinary aldosterone-to-creatinine ratio after fludrocortisone suppression has recently been described and

appears to be another promising diagnostic tool. The disease is often suspected only after the finding of an adrenal mass by ultrasonography.

Initial treatment should be directed towards alleviation of hypertension and hypokalemia by using an aldosterone antagonist (spironolactone, initial dose 1-2 mg/kg BID) and a calcium channel blocker (amlodipine besylate 0.625-1.25 mg/cat SID), and substituting potassium as needed. Subsequent adrenalectomy is the treatment of choice for animals without tumor metastasis. In the few cases described in the literature, as well as in the cases seen at our hospital, hypertension resolved after surgery. In cases in which adrenalectomy is not feasible (e.g. metastasized tumor, bilateral tumor or hyperplasia), medical treatment with spironolactone and amlodipine besylate should be continued. The two drugs combined seem to lead to resolution of hypertension in most cases.

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